Grant# HD44406

Center Director: John O. Delancey, M.D.

Center Overview

This proposal seeks to improve care for the women who suffer the priority health conditions of urinary incontinence and pelvic organ prolapse. These problems arise due to women's unique role in giving birth and, therefore, occur much less often in men. Each year 3 million women deliver babies and 11 % of women need surgery for incontinence and prolapse. A lack of basic understanding of the mechanisms involved in these conditions and their implications for treatment impedes progress. We propose a SCOR to unite 5 existing multidisciplinary researchers and to add 4 new investigators to expedite development of new knowledge needed to improve treatment and prevention. Project 1, "Biomechanics" will test hypotheses concerning basic mechanisms of pelvic floor structure and function. It will analyze the mechanical arrangement and properties of the components of the pelvic floor as well as how vaginal birth damages their integrity. Project 2, "Clinical Mechanisms" will test continent and stress incontinent women to detect the unique failure of component parts that, singularly and in combinations, are associated with stress incontinence. Project 3, "Treatment Selection" will identify the effects of birth induced muscle damage in women with stress incontinence and from these data, build and test a model to determine which defects will predict success or failure of pelvic muscle treatment. Core A, Administrative/Human Subjects/Biostatistics core provides project support by recruiting subjects, compiling and analyzing data and protecting subject safety. In Core A, two study groups will be formed concerning 1) Gender Impact and 2) Basic Sciences Futures to discuss expanding the issues raised by this research. Core B, Measurement & Imaging will provide technical support for the projects along with integrated image analysis for 2 and 3 dimensional spatial data gathered across projects. This research will produce needed insights to help women with pelvic floor dysfunction.

Principal Investigator: James A. Ashton-Miller, Ph.D.

Project 1: Pelvic Floor Biomechanics and Birth Injury

NIDDK's Bladder Progress Review Group and NICHD workshop on Female Pelvic Floor Disorders have identified the lack of an understanding of the biomechanics of the female pelvic floor as a critical knowledge gap impeding research. The aims of this research are therefore to use human anatomical material to: (1) Characterize the mechanical properties and architecture of the passive and active structural elements comprising the female pelvic floor, the vesical neck support system, and the urethra; (2) Test the null hypotheses that neither age nor parity affects the number of (a) striated muscle cells, (b) smooth muscle cells, (c) number of nerves or the elastic moduli of passive tissue elements; (3) Develop a 3-D biomechanical pelvic floor model with representations of fetal head geometry, muscles and nerves based on anatomic material and probabilistic atlas data from 30 young, 30 middle-age, 30 elderly continent women MR data; (4) Develop a three-muscle-layer 3-D biomechanical model of the urethra and compare predicted values to urethral closure pressure behavior measured in 90 Project 1 nullipara, as well as Project 2 and 3 patients; (5) Use 2- and 3-D lumped parameter and finite element models to simulate different aspects of vaginal birth and test hypotheses that (a) largest muscle strain occurs in the nulliparous' puboperineus muscle, and (b) largest nerve strain occurs in the nulliparous' inferior hemorrhoidal nerve; analyze effects of normal vs. abnormal fetal head size and orientation (e.g. occipito-posterior), rapid-descent (forceps) vs. slow second stage (epidural) as well as geometry, timing and extent of episiotomy. These observations will yield insight into pelvic floor biomechanics that can help direct future research into these long-neglected but important issues.

Principal Investigator: John O. Delancey, M.D.

Project 2: Which Pelvic Floor Defects Cause Stress Incontinence?

The lack of scientific understanding of the basic mechanism underlying stress urinary incontinence (SUI) is impeding preventing, treatment and research. New findings reveal birth-induced injuries that may explain the higher prevalence of this condition in women than men. We propose studying women with SUI who present for treatment to determine the type and location of pelvic floor failure responsible for this priority condition in women's health. Our hypothesis maintains that SUI occurs through individual defects and specific combinations of defects. We will quantify and compare vesical neck support and urethral sphincter function in classes; women with SUI, and controls; similar women without SUI, to test this hypothesis. Aim 1: Using these data we will demonstrate that the occurrence of SUI is a function of both support stiffness and sphincter constriction and that the threshold for having SUI is an interaction of these two types of measures that explains SUI better than either sphincter or support function alone. Aim 2: Define the anatomic abnormalities that are responsible for these functional problems. Using MR imaging we will show that, 1) Loss of support involves loss of levator and bulk measurable on MRI as decrease in size of the levator ani and/or breaks in connective tissue supports and 2) Sphincteric weakness results from quantifiable loss of sphincter bulk in the smooth and striated sphincter muscles. Correlation between anatomic measurements and functional parameters listed in the primary hypotheses will determine the cause of functional abnormalities. Aim 3: Evaluate other personal and medical variables that may influence incontinence. The importance of this research lies in its providing insights that should help form the basis for rational treatment selection in women with SUI, devise injury prevention, understand where deterioration occurs, and form a basis for organ, cell, and molecular research into these disease processes.

Principal Investigator: Janis M. Miller, RN, Ph.D.

Project 3: Selection Criteria for Pelvic Muscle Therapy in Stress Urinary Incontinence

The long-term goal is to develop an effective behavioral therapy for stress urinary incontinence (SUI). Estimated prevalence rates of urinary incontinence range from 15-43% of women, with SUI as the most prevalent. The project will test Knack therapy, a self-help treatment for SUI that teaches women a pelvic floor muscle contractions simultaneously with a event known to trigger leakage. By doing so, momentary closure pressure is imposed on the urethra and risk for leakage is immediately reduced. This proposal aims to develop and test, in a general population of women with SUI, a model for predicting who will succeed in a costly surgery and time consuming Kegel's exercises). Specific Aims are to: (1) develop a logistic regression model to predict success with the Knack, (2) validate the model by determining the proportion of people who succeed according to who is predicted to succeed, and (3) develop long-term effectiveness of the Knack (1-year). The project will be implemented in three phases: model development (n=160 women), model validation (n approximately 160), and long-term follow-up of women who demonstrate response. The short-term outcome of "positive response" is defined as able to reduce leakage during coughing to under 2 ml or 50% decrease from baseline (whichever is more stringent). This will be evaluated immediately and at 1 month. Leakage is evaluated in simple fashion with a paper towel test in the clinic. Long-term success (3-month and 1-year) is defined both by the paper towel test criteria and by documentation of at least 50% reduction of leakage in diary to reflect success at home. ROC curve analysis will be used to analyze model data, t-test and descriptives to analyze response. Anticipated results include that 1) the treatment group will demonstrate significantly less urine leakage than a control group immediately post-instruction and at 1-month follow-up; and 2) over time (1-, 3-, and 12-months) at least 80% of women selected by the predictive model who receive the Knack intervention will reach and sustain a greater than 50% reduction in urine loss from baseline.

Principal Investigator: James A. Ashton-Miller, Ph.D.

Core: Measurement and Imaging

The Measurement and Imaging Core will integrate and analyze the urodynamic and vesical neck (VN) kinematic data from 690 women for Projects 1, 2 and 3. It will provide each project with the standardized data set required. Using ultrasound images determine, in a (local) symphyseal coordinate system, vesical neck displacement vectors (VNC, VNV, VNK) for each of the Multi-component Pelvic Floor Assessment activities (deep cough, Valsalva, maximum Kegel) from the resting position (Aim 1). The resulting vesical neck support stiffness (VNS) during cough and Valsalva maneuvers will be calculated and provided to each project. Using magnetic resonance (MR) image reconstruction, individual Project 2 patient pelvic floor geometry will be compared with the age-appropriate with the age-appropriate probabilistic atlas of healthy young, middle-age or old pelvic floors, each created for Project 1 using existing scans of 30 continent women between 20 and 74 years of age (Aim 2). Lastly (Aim 3), the Core will provide bioengineering and technical support to each project maintaining the hardware and software of the instrumented speculum used to measure levator ani contractile maintaining the hardware and software of the instrumented speculum used to measured levator ani contractile properties, and analyze and prepare that data (LAR and LAMVC) on levator ani muscle force for all 690 women.